

CONTINUING MEDICAL EDUCATION

Infective Endocarditis—Prophylaxis, Diagnostic Criteria, and Treatment

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SUMMARY

Background: Despite important medical advances, infective endocarditis (IE) is still a disease with high morbidity and mortality. Its prophylaxis, diagnosis, and treatment are still a major challenge in clinical practice.

Methods: Selective literature review based on the current German and European guidelines and a PubMed search from 2004 onward.

Results: Essential requirements for the rapid diagnosis and specific treatment of IE are the echocardiographic demonstration of endocardial disease and the identification of the causative organism by blood culture. The modified Duke criteria have made the diagnosis more objective but are not a replacement for clinical judgement. It should be borne in mind, when the initial empirical treatment is chosen, that *Staphylococcus aureus* is currently the most common causative organism. If diagnostic criteria are met that suggest a methicillin-resistant *S. aureus* infection, then glycopeptide antibiotics are still the standard treatment. Newer agents such as daptomycin can be considered as an alternative, as suggested by recent studies and in view of the increasing frequency of impaired vancomycin susceptibility. Early surgical treatment should be considered for patients who are likely to encounter further complications along their clinical course. According to the current recommendations, antibiotics should be given for endocarditis prophylaxis only to patients about to undergo one of a small number of explicitly defined procedures, who would otherwise be at a high risk of major illness or death. The purpose of this restriction is to make prophylaxis more efficient.

Conclusion: IE remains a potentially lethal infectious disease that can be treated effectively only by physicians from multiple disciplines working in collaboration.

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Infective endocarditis is an endovascular infection, usually caused by bacteria, that affects not only the native heart valves but also, with increasing frequency, intravascularly implanted foreign materials such as valvular prostheses or pacemaker electrodes. Despite major advances in diagnosis and treatment, infective endocarditis (IE) remains a disease with high morbidity, and with a mortality of 20% to 30%. Its precise incidence in Germany is unknown. In France, a neighboring country, its incidence is 30 cases per million inhabitants per year (1).

The learning objective of this article for the reader is to acquire knowledge of

- the rationale behind the new guidelines for endocarditis prophylaxis,
- the fundamentals of antimicrobial therapy, including consideration of the changing spectrum of pathogens and of new antibiotics, and
- the importance of interdisciplinary collaboration, with contributions from cardiology, microbiology, infectious disease, and cardiac surgery.

One cause of the high mortality of infective endocarditis is the long latency from the onset of symptoms to the definitive diagnosis of IE and the initiation of appropriate treatment (Benetka O, Block M, Sangha O et al.: Clinical course of infective endocarditis in the late nineties: preliminary results of the ALKK endocarditis registry [Abstract]. Eur Heart J 1999; 20 [Suppl]: 362). A further problem arises from the high percentage of cases of infective endocarditis with negative cultures, in which specifically tailored antibiotic therapy is not possible. This problem is especially severe in Germany. In addition to the underlying pathogen, many individual patient parameters determine the clinical course of the disease. Often, no causal chain can be established linking infective endocarditis to a bacteremia-inducing event; in 80% of cases, no precipitating cause for IE can be identified. Even after dental procedures, the risk of

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Epidemiology

The incidence of infective endocarditis is 30 per million persons per year, with a mortality of 20% to 30%. It is noteworthy that the latency from the onset of the first symptoms to diagnosis is about one month.

BOX 1

Patients at highest risk for a complicated or lethal course of infective endocarditis (from [2], without modification)

- Patients with a valvular prosthesis (mechanical or biological):
 - Patients with reconstructed valves containing alloprosthetic material in the first 6 months after surgery^{1,2}
- Patients who have previously had endocarditis
- Patients with congenital heart defects:
 - Cyanotic heart defects that have not been surgically corrected, or that have been treated palliatively with the creation of a systemic-to-pulmonary shunt
 - Heart defects that have been treated surgically with the implantation of conduits (with or without valves), or residual defects, i.e., turbulent blood flow in the area of the prosthetic material
 - All heart defects that have been treated surgically or interventionaly, in the first six months after the procedure²
- Heart-transplant recipients who have developed a cardiac valvulopathy

¹The DGK/PEG position paper differs on this point from the AHA guidelines.

²After 6 months, adequate endothelialization of prostheses is assumed to have occurred.

developing IE is only one in multiple tens of thousands of procedures, depending on the patient's risk profile.

The purpose of this article is to illuminate the current state of the diagnostic evaluation, treatment, and prophylaxis of IE (1, 2). It is based on the current German and European guidelines, as well as on literature from 2004 onward that was retrieved through a PubMed search.

Prophylaxis

The need for the prophylactic administration of antibiotics to prevent infective endocarditis after medical procedures has been a matter of controversy from the moment it was first postulated. Neither the effectiveness nor the individual benefit of prophylaxis has yet been studied in a prospective, randomized trial. While experimental work in animals has shown that, under controlled conditions, antibiotic prophylaxis can indeed prevent IE, the conclusion of a current Cochrane meta-analysis is that the effectiveness of penicillin in preventing IE after dental procedures (for example) remains unclear (3). Furthermore, the estimated risk of IE after medical procedures is, in general, so low that one may suspect that multiple

tens of thousands of patients would have to be treated with antibiotics in order to prevent a single case of endocarditis, even if antibiotic prophylaxis were assumed to be 100% effective (2).

The above considerations have now led to a paradigm shift (4) in the current guidelines, which reserve the use of antibiotic prophylaxis for patients who would be at high risk for a particularly severe disease course, or a fatal outcome, in case they developed IE (*Box 1*). The procedures after which prophylaxis is recommended have also been markedly restricted (*Box 2*). In this way, an attempt is being made to proceed with care, in view of the presumably low efficiency of antibiotic prophylaxis—i.e., the unfavorable relationship of its cost, potential risks, and individual benefit—and its questionable effectiveness, yet without subjecting patients whose prognosis is especially poor to a potentially avoidable danger. The recommended antibiotics are aminopenicillins for first-line therapy, followed by clindamycin in case of penicillin intolerance.

It has been found that the overwhelming majority of endocarditis cases have no antecedent history of any of the medical procedures classically thought to increase the risk of IE, even when these procedures are sought as broadly and inclusively as possible (5, Benetka O, Block M, Sangha O et al.: Clinical course of infective endocarditis in the late nineties: preliminary results of the ALKK endocarditis registry [Abstract]. Eur Heart J 1999; 20 [Suppl]: 362). Even everyday activities in the oral area, such as tooth-brushing, flossing, or the chewing of food, can lead to transient bacteremia, depending on the state of the patient's teeth. In view of these facts, the current guidelines include a general recommendation for the maintenance of good oral hygiene.

Diagnostic evaluation

History, clinical findings, and laboratory parameters

In Germany, the diagnostic latency, i.e., the interval from the onset of symptoms to the definitive diagnosis of IE, averages longer than one month (Benetka O, Block M, Sangha O et al.: Clinical course of infective endocarditis in the late nineties: preliminary results of the ALKK endocarditis registry [Abstract]. Eur Heart J 1999; 20 [Suppl]: 362). The classic cardinal symptoms, such as a newly arisen or worsened heart murmur in a patient who has not been examined before by a cardiologist or nonspecific symptoms such as fever, subfebrile temperature, weight loss, night sweats, prostration, or myalgia, are often difficult to assess. Often, the initial

Endocarditis prophylaxis

The use of antibiotics for endocarditis prophylaxis in procedures that can cause bacteremia is controversial, because the current scientific evidence is inadequate either to support or to invalidate current practice.

Indications for endocarditis prophylaxis

Endocarditis prophylaxis is now recommended only for patients who would be at high risk of having a complicated or lethal disease course in case they developed endocarditis.

symptoms are already manifestations of complications that have set in, such as progressive dyspnea due to destruction of a heart valve, with marked volume overloading of the heart. Septic emboli from vegetations can often produce neurological manifestations; they arise in up to 30% of cases (6), often as an initial manifestation.

Whenever such symptoms arise, IE should be included in the differential diagnosis, particularly if risk factors are present, e.g., a cardiac valvular prosthesis or intravenous drug abuse.

Vascular and immunological phenomena can also be seen:

- Osler's nodes (subcutaneous hemorrhagic nodules indicating immune complex vasculitis or septic embolism);
- splinter hemorrhages (hemorrhage under the fingernails);
- Janeway lesions (hemorrhage of the palms and soles caused by immune complexes);
- glomerulonephritis.

The usual laboratory parameters of inflammation, such as leukocytosis with a left shift, an elevated concentration of C-reactive protein, and an accelerated erythrocyte sedimentation rate, are basically nonspecific and are only of use in pre-selected patients with corresponding clinical manifestations. An elevated serum procalcitonin concentration may be a sensitive indicator of systemic infection, but it is not specific for IE either.

Echocardiography

The pictorial, morphological demonstration of suspect lesions by transthoracic and transesophageal echocardiography (TTE and TEE) plays a central role in the diagnostic evaluation of infective endocarditis. Whenever there is reason to consider this diagnosis, an immediate examination with transthoracic echocardiography is required. Except in cases of right-heart endocarditis, TEE is always more sensitive than TTE (7); thus, TEE should always be performed, particularly if the image quality on TTE is poor, if the patient has a prosthetic heart valve, or if TTE has yielded a positive finding (*Figure*). A single negative TEE result does not rule out infective endocarditis, however. If clinical suspicion remains, the study should be repeated in six to ten days.

Both transthoracic and transesophageal echocardiography yield only morphological information. Therefore, both methods are inadequately specific in themselves. Diagnostic specificity is achieved in combination with the accompanying clinical and microbiological findings (8).

The clinical manifestations of endocarditis

The clinical manifestations are often nonspecific, such as fever, weight loss, and night sweats. Septic emboli can cause neurological manifestations. Thus, the possibility of infective endocarditis should be considered whenever neurological abnormalities are found in a patient with an unexplained fever.

BOX 2

Procedures after which antibiotic prophylaxis is recommended for patients who are at high risk for a complicated or lethal course of infective endocarditis (from [2])

- Dental procedures involving manipulation of the gingiva or the periapical region of the teeth, or perforation of the oral mucosa
- Dental procedures with intraligamentous anesthesia
- Procedures in which the mucosa of the upper respiratory tract is incised, e.g., tonsillectomy and adenectomy

Procedures after which no antibiotic prophylaxis is recommended

- Procedures on the skin and soft tissues
- Procedures on the gastrointestinal tract, including gastroscopy and colonoscopy with biopsy
- Procedures on the urogenital tract, including cystoscopy

In general, the following considerations hold: In any procedure involving infected tissue, the infection should be treated. For patients at high risk for a complicated or lethal course of infective endocarditis, the prophylactic antibiotic regimen should be chosen to cover the typical infectious pathogens arising from the site in question (e.g., gastrointestinal tract: enterococci).

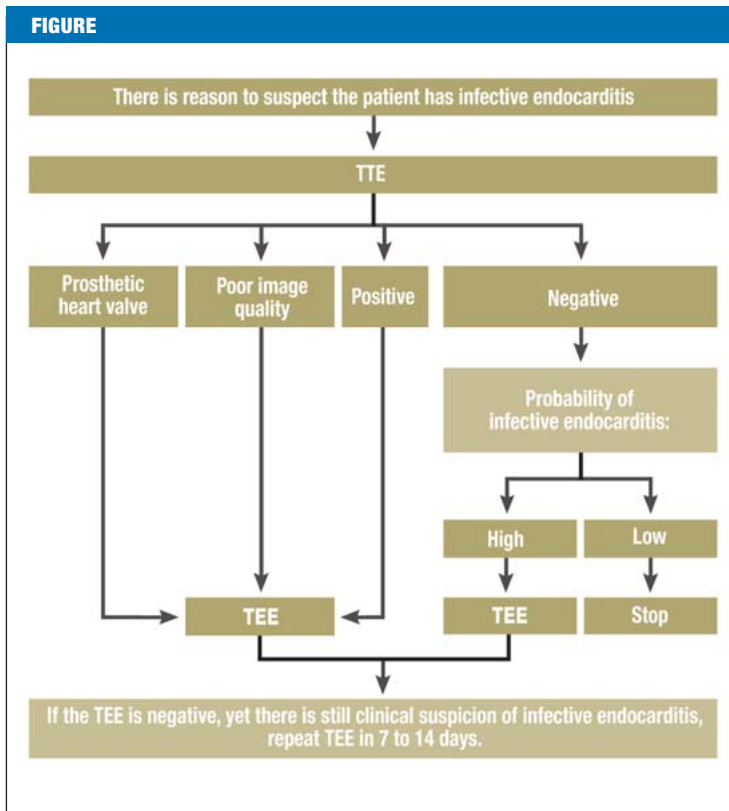
In addition to the demonstration of the typical, so-called vegetations (i.e., bacterially colonized thrombi adherent to the endocardium), the size of the vegetations is an oft-discussed parameter, as multiple studies have shown that vegetation size is correlated with the occurrence of central and peripheral embolization, or even with patient survival. Nonetheless, the measurement of vegetation size has not been standardized, and its variability among examiners is, therefore, considerable.

Equally important is the echocardiographic assessment of tissue destruction due to infection, which can take the form of abscesses, fistulae, perforations, avulsion of chordae tendineae, or prosthesis dehiscences, and the resulting valvular or paravalvular insufficiency or intracardiac shunt. An assessment of left- and right-ventricular function is also obligatory and can provide an early indication of cardiac overloading due to a structural anomaly, or of septic cardiomyopathy.

Once the diagnosis has been established, weekly echocardiographic follow-up should be performed, because local progression can occur even if the patient

The role of echocardiography

Echocardiography is the method of choice for the demonstration of endocardial involvement. Transesophageal echocardiography is more sensitive than transthoracic echocardiography.



The use of echocardiography when there is reason to suspect infective endocarditis; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; modified from (1)

has become afebrile. A follow-up study may be needed even earlier if the patient's clinical condition worsens, so that complications can be detected in timely fashion.

Identifying the causative organism

In addition to echocardiographic diagnosis, the identification of the causative organism is a further prerequisite for targeted therapy. The proper taking of blood cultures is essential before antimicrobial therapy is begun. Three sets of aerobic and anaerobic blood cultures should be taken independently by peripheral venipuncture after adequate disinfection. As bacteremia is assumed to be continually present, there is no need to time the blood cultures in any particular relation to the patient's body-temperature curve.

Identification of the infective organism

Three sets of blood cultures (aerobic and anaerobic) should be drawn from a peripheral vein, after adequate disinfection of the skin, before antibiotics are given. The patient's body temperature at the time of blood drawing is irrelevant.

In 10% to 30% of cases, the blood cultures remain negative. It is unclear, however, whether such patients have a worse prognosis than those in whom the causative organism is identified. The main cause of negative blood cultures is pretreatment with antibiotics (9). Thus, when a patient with negative blood cultures is clinically stable, a temporary pause in antibiotic treatment (for at least 48 hours) should be considered before blood cultures are drawn again.

A further reason for a negative blood culture may be the presence of microorganisms that are difficult to culture, such as fungi, *Bartonella* spp., *Coxiella* spp., and pathogens of the so-called HACEK group, which includes *Haemophilus* species (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, and *Haemophilus paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species. It is essential, therefore, that the suspected diagnosis of infective endocarditis be noted on the laboratory requisition, so that appropriate testing can be performed. In addition, modern serological methods can be used to assist in the identification of pathogens that are hard to culture. The clinical value of molecular-biological methods, such as the polymerase chain reaction (PCR), for the detection of infectious pathogens in whole blood or serum has not yet been fully determined, however, because of the lack of standardization and the unclear significance of the DNA findings that are obtained.

Diagnostic criteria

The so-called Duke criteria were introduced in 1994 (10) and were originally conceived for the objectification of the complex clinical manifestations and findings in infective endocarditis for the purposes of scientific studies. They were rapidly implemented in everyday clinical practice as well. They were the first diagnostic criteria to include echocardiography as a morphological parameter, thereby significantly improving diagnostic sensitivity, while preserving nearly the same high degree of specificity as earlier sets of criteria. The Duke criteria characterize the probability that IE is present as "definite," "possible," or "excluded." The main criteria are the identification of the causative organism and the echocardiographic demonstration of endocardial involvement. Additional criteria include, e.g., fever, vascular involvement, or a predisposing heart disease. Since the initial publication of the Duke criteria, various modifications have been proposed, with the purpose of increasing their sensitivity. The extended Duke criteria

Diagnostic criteria

The Duke criteria enable the diagnosis to be made objectively but are not a substitute for clinical judgment. The modifications in the Duke criteria to date have increased their sensitivity, but lessened their specificity.

of Li et al. (11) are now generally accepted: these consider *Staphylococcus aureus* bacteremia to be a main criterion, as a positive blood culture for *S. aureus* is associated with endovascular infection in up to 15% of cases (Boxes 3a and 3b). Whenever new parameters are introduced, however, it must be borne in mind that increased sensitivity often comes at the price of diminished specificity. Thus, a current meta-analysis including 3557 patients has shown that the rise in sensitivity brought about by the Li modifications is associated with a comparable fall in specificity (Neuerburg CK, Breuckmann F, Buhr C, Philipp S, Eggebrecht H, Kordish I, Böse D, Naber CK: Duke-Kriterien zur Diagnostik der infektiösen Endokarditis: Metaanalyse von 3557 Fällen und Ergebnisse einer prospektiven Studie [Abstract]; Clin Res Cardiol 2007; [Suppl 1] V1148).

In summary, diagnostic criteria are not a substitute for rational clinical judgment, particularly when the blood cultures are negative, when prosthetic valves or pacemaker electrodes are infected, or when the endocardium of the right side of the heart is affected (12).

Principles of antibiotic therapy

The prognosis of infective endocarditis depends on many factors, including the site of infection, the underlying pathogen, the local defenses against infection, the involvement of foreign material, and the interval from the onset of symptoms to the establishment of the diagnosis (1). In general, right-sided endocarditis is less commonly associated with cerebral complications and can be treated conservatively with a higher success rate than left-sided endocarditis. Endocarditis involving a prosthetic heart valve tends to require surgical intervention earlier, and more often, than native-valve endocarditis. A *Staphylococcus aureus* infection usually takes a more severe clinical course than an infection with *Streptococcus* spp.

The fundamental goal of therapy—the eradication of the pathogen from the infected tissue—is made more difficult to achieve by specific and nonspecific defense mechanisms, e.g., biofilm formation and increasing tolerance or resistance to various antibiotics.

If the patient's general condition is critical, then empirical, broad-spectrum antimicrobial therapy is begun as soon as blood cultures have been drawn. The early initiation of appropriate antibiotic therapy is very important, because it can not only control the local infection, but also lessen the risk of complications such as septic embolization (13).

Antibiotic treatment

After blood cultures are drawn, broad-spectrum combination therapy with antibiotics should be initiated, based on the spectrum of possible infective organisms and the particular structure that is involved (native valve, prosthesis, etc.). Once the microbiological results are known, the antibiotic treatment is adapted accordingly.

BOX 3a

The Duke criteria (10) and the modified Duke criteria (11)

Pathological criteria

Histological or bacteriological demonstration

Major criteria

- Positive blood cultures
 - Typical infective organism for endocarditis
 - Persistently positive blood cultures
- Endocardial involvement
 - Echocardiography: oscillating structures, abscess, new valve dehiscence
 - New valvular insufficiency
 - Worsening of pre-existing valvular insufficiency

► Modification—also:

- Positive Q fever serology
- *S. aureus* bacteremia

Minor criteria

- Predisposing heart disease
- Fever >38°C
- Vascular phenomena
- Immunological phenomena
- Microbiological demonstration (not a main criterion)
- Diagnosis suspected on the basis of echocardiography (not a main criterion)

► Modification—no longer an additional criterion:

- Diagnosis suspected on the basis of echocardiography (not a main criterion)

A distinction should be made between native-valve endocarditis and prosthetic-valve endocarditis, which can, in turn, be either early (less than 1 year after valve replacement) or late (more than one year after valve replacement). A different spectrum of pathogens is to be expected in each of these cases (1).

The spectrum of causative organisms in native-valve endocarditis and late prosthetic-valve endocarditis mainly consists of methicillin-sensitive *S. aureus* strains, various streptococcal species, and *Enterococcus faecalis*. Early prosthetic-valve endocarditis, on the other hand, is often due to methicillin-resistant *S. aureus* strains, coagulase-negative staphylococci, or gram-negative pathogens (14).

Native-valve endocarditis

In native-valve endocarditis and late endocarditis after valve replacement, the most common infective organisms are methicillin-sensitive *S. aureus* strains, various streptococcal species, and *Enterococcus faecalis*.

BOX 3b

Categories of the Duke criteria and the modified Duke criteria

Categories of the Duke criteria (10) and of the modification (11)

Definite

- Pathological criteria met
- Or 1 major criterion met
- Or 1 major and 2 minor criteria met
- Or 5 minor criteria met

Possible

- All cases that are not classified as definite or excluded

▷ **Modification**

- 1 major and 1 minor criterion met
- Or 3 minor criteria met

Rejected

- Probable alternative diagnosis
- Resolution of symptoms four days after initiation of antibiotic treatment
- No definitive histological or bacteriological confirmation at surgery or autopsy

Current aspects of antibiotic therapy

Treatment should be started on an empirical basis, then modified once resistance data have been obtained. The choice of a suitable antibiotic should take the minimal inhibitory concentration (MIC) into account and not merely be based on a discrete classification of antibiotic sensitivity, e.g., into the three categories "sensitive," "intermediate," and "resistant." This holds particularly for treatment with glycopeptides: "vancomycin resistance," though often discussed, has been seen only rarely to date, including among *S. aureus* (VRSA), while the true knot of the problem lies in *S. aureus* strains that are vancomycin-intolerant, i.e., that have only intermediate sensitivity to vancomycin (VISA) (15). In such cases, treatment can be appropriately guided only by the precise determination of resistances, along with adequate monitoring of serum trough levels; according to the current recommendations, these should lie in the range of 15–20 µg/mL and not, as previously recommended, 5–10 µg/mL (16) (Table).

Although most previously published guidelines

recommended combination therapy with beta-lactams and gentamicin, this recommendation must be viewed critically, particularly with regard to the treatment of staphylococcal infections. This is so even though it was, indeed, shown in small randomized trials, more than 20 years ago, that the combination of nafcillin and gentamicin can lead to a more rapid defervescence in IE patients.

More recent meta-analyses show that combination therapy with gentamicin is not clinically superior to beta-lactam monotherapy (17, 18); it leads, instead, to significantly elevated nephrotoxicity. In the guideline of the American societies, which is the one most recently published, combination therapy with gentamicin is designated as optional for the treatment of staphylococcal infection (19). This contrasts with the finding, from a Swedish registry, that the survival of patients with culture-negative IE is significantly improved if they are given combination therapy with gentamicin (20).

For the treatment of infective endocarditis due to methicillin-resistant streptococci, not just vancomycin, but also newer agents are currently being discussed. The lipopeptide daptomycin, for example, has been studied in a prospective, randomized trial in patients with right-heart endocarditis and has been approved for this indication (21). The most interesting discovery is that this agent, unlike vancomycin, was at least as effective as the combination of a beta-lactam antibiotic and gentamicin in the treatment of methicillin-resistant staphylococcal infection.

While daptomycin has been found effective against secondary pulmonary abscesses caused by the embolization of infected vegetations, it is of no use against primary pulmonary infections, because the agent interacts with pulmonary surfactant. The nephrotoxicity of daptomycin was markedly less than that of comparable treatment with a combination of vancomycin, or a semi-synthetic penicillin, with gentamicin. Daptomycin was found to elevate the serum creatine kinase (CK) concentration; the latter should, therefore, be monitored when daptomycin is given. In a small number of cases in this study, the minimal inhibitory concentration (MIC) of daptomycin was found to rise under treatment. Although this finding is of uncertain significance, it indicates the possible development of resistance and thus requires further, careful study (21).

The oxazolidinone linezolid has also been used successfully in a number of cases of IE (22), but there are, as yet, no prospective data on this form of treatment.

New antibiotics

Daptomycin has been approved for the treatment of right-heart endocarditis due to *S. aureus*. In the licensing study, this agent was found to be less nephrotoxic than standard treatment. One should take heed of the possibility of CK elevation during treatment and of the potential development of tolerance or resistance.

Gentamicin

There are no clinical endpoint studies supporting the combined use of gentamicin and beta-lactam agents. As this combination is highly nephrotoxic, it should be viewed as being no more than optional for the treatment of staphylococcal infections.

TABLE

Antibiotics commonly used to treat infective endocarditis

Microorganisms	Antibiotic	Dosage	Duration
Staphylococcus spp.	Flucloxacillin or oxacillin If penicillin-allergic: vancomycin* ¹ Optional: with gentamicin* ^{2,3}	12 g/d in 4–6 doses 30 mg/kg/d in 2 doses 3 mg/kg/d in 2–3 doses	4–6 weeks IV 4–6 weeks IV 3–5 days IV
MRSA and prosthetic valves	Vancomycin with rifampicin* ⁴ and gentamicin* ²	30 mg/kg/d in 2 doses 1200 mg/d in 2 doses 3 mg/kg/d in 2–3 doses	≥6 weeks IV ≥6 weeks PO 2 weeks IV
Enterococcus spp.	Amoxicillin or ampicillin with gentamicin* ²	200 mg/kg/d in 4–6 doses 3 mg/kg/d in 2–3 doses	4–6 weeks IV 4–6 weeks IV
Oral streptococci and group D streptococci (MIC for penicillin <0.125 mg/L)	Penicillin G or amoxicillin or ceftriaxone If penicillin-allergic: vancomycin* ¹	12–18 MU/d in 6 doses 100 mg/kg/d in 4–6 doses 2 g/d in a single daily dose 30 mg/kg/d in 2 doses	4 weeks IV* ⁵ 4 weeks IV* ⁵ 4 weeks IV* ⁵ 4 weeks IV
Oral streptococci and group D streptococci (MIC for penicillin ≥0.5 mg/L)	Penicillin G or amoxicillin If penicillin-allergic: vancomycin* ¹ with gentamicin* ²	12–18 MU/d in 6 doses 200 mg/kg/d in 4–6 doses 30 mg/kg/d in 2 doses 3 mg/kg/d in a single daily dose	4 weeks IV 4 weeks IV 4 weeks IV 2 weeks IV

¹For more information, the reader is directed to the guideline of the European Society of Cardiology, which is due to be published shortly

²Weekly checking of the serum drug level and of renal function is recommended

³Optional in this situation because of inadequate demonstration of clinical benefit, along with high nephrotoxicity

⁴The clinical benefit of rifampicin in this situation has not been rigorously shown, but it is usually given nevertheless, because of its presumed high biofilm penetration.

⁵Or two weeks, when combined with gentamicin 3 mg/kg/d given in a single IV daily dose*²

MIC = minimal inhibitory concentration.

Continuation of treatment on an outpatient basis for selected patients

In view of the high risk of complications in the first two weeks after diagnosis, outpatient treatment in this period should be viewed with the utmost caution. As long as no complications have arisen by the end of this period, such as acute valvular insufficiency, severe septic embolization, or high-grade atrioventricular block, it may be possible to continue treatment on an outpatient basis, particularly in native-valve endocarditis due to penicillin-sensitive streptococcal strains (23). The patients must be selected carefully, and good compliance is essential. Weekly outpatient follow-up in the treating hospital should be arranged, in order to monitor the success of treatment and modify the treatment strategy as needed (24).

All patients with infective endocarditis due to a pathogen that is known from experience to be associated with a high risk of complications (such as *S. aureus*, multiply resistant staphylococci, or enterococci) should,

as a rule, remain hospitalized for the duration of their treatment.

Surgical treatment

The first operations to treat infective endocarditis were performed by Kaye in the 1960s; since then, surgical treatment has become well established, although there have been no randomized, prospective trials to confirm its benefit. In particular, the optimal timing of surgery remains unclear.

The classic indications for early surgery are endocarditis with severe heart failure, uncontrolled infection despite appropriate antibiotic therapy with persistent fever and/or bacteremia, local spread of infection with the formation of perivalvular abscesses or fistulae, septic embolization, new onset of atrioventricular block, prosthetic valve endocarditis, and endocarditis in the presence of a pacemaker or intracardiac defibrillator (ICD) (6, 25. e1).

The acute onset of severe aortic or mitral insufficiency accompanied by pulmonary edema or persistent

Outpatient treatment

In view of the high risk of complications in the first two weeks after diagnosis, outpatient treatment in this period should be viewed with the utmost caution.

Surgical treatment

Surgical treatment should not be viewed as the last resort when conservative treatment fails, but rather as an important component of the overall therapeutic strategy.

cardiogenic shock is an indication for immediate surgery.

In mitral valve endocarditis, valvular reconstruction should be the goal whenever possible, in order not to introduce alloprosthetic material to the area while a florid infection is still present (e2). Abscesses and fistulae should be resected in toto and, if necessary, covered with a pericardial patch. In many cases, however, complete surgical repair of the infected focus is only realizable by means of a valve replacement, because the technical prerequisites for valve reconstruction are not fulfilled (e1).

After surgery, antimicrobial therapy must be continued for at least two weeks. If infected foci are found intraoperatively, or if a culture of the valve is positive, then the total duration of therapy should be 4 to 6 weeks or more (1). In cases of endocarditis involving an implanted pacemaker or ICD, the infective organism must be completely eradicated before a new system is implanted (e3).

Conclusions

The essential prerequisites for the rapid diagnosis and specifically targeted treatment of infective endocarditis are the morphological demonstration of endocardial involvement by echocardiography and the identification of the underlying pathogen with properly drawn blood cultures. The modified Duke criteria enable the diagnosis to be made more objectively, but are not a substitute for clinical judgment. When an initial, empirical antibiotic therapy is chosen, it should be borne in mind that *S. aureus* is now the most common causative organism in infective endocarditis. If criteria are met that suggest the presence of infection with a methicillin-resistant strain of *S. aureus* (MRSA), treatment with a glycopeptide antibiotic is still the standard. In view of the current scientific evidence and the increasing prevalence of vancomycin intolerance, the use of newer substances such as daptomycin can also be considered. For cases with a complicated clinical course, surgical treatment is indicated.

Current recommendations restrict the use of antibiotics for endocarditis prophylaxis to patients undergoing one of a small number of explicitly defined procedures who would otherwise be at a high risk of major complications or death from endocarditis. The purpose of this restriction is to make prophylaxis more efficient.

Conflict of interest statement

PD Dr. Naber is a member of the advisory boards of the Novartis and Astellas companies. The other authors declare that they have no conflict of interest as defined by the International Committee of Medical Journal Editors.

Indications for surgical treatment

Surgery should be performed without delay if infective endocarditis cannot be controlled by conservative treatment, or in case of cardiac decompensation, abscess formation, or recurrent embolization.

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Conclusion

The essential prerequisites for the rapid diagnosis and specifically targeted treatment of infective endocarditis are the morphological demonstration of endocardial involvement by echocardiography and the identification of the underlying pathogen with properly drawn blood cultures.

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For e-references please refer to:
www.aerzteblatt-international.de/ref2809

A case report is available at:
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Further Information on CME

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The solutions to the following questions will be published in issue 37/2009. The CME unit "Constipation: Pathophysiology, Diagnosis, and Treatment" (issue 25/2009) can be accessed until 31 July 2009.

For issue 33/2009 we plan to offer the topic "Gastroenteritis in Childhood."

Solutions to the CME questionnaire in issue 21/2009:

Zopf Y et al.: Differential Diagnosis of Food Intolerance.
Solutions: 1a, 2b, 3e, 4d, 5d, 6b, 7a, 8c, 9d, 10c

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the current mortality of infective endocarditis?

- a) 5–10%
- b) 20–30%
- c) 50–60%
- d) 70–80%
- e) Over 90%

Question 2

To which group of patients, according to current guidelines, should antibiotics be given as prophylaxis against endocarditis?

- a) Patients with mitral insufficiency
- b) Patients with mitral stenosis
- c) Patients with aortic insufficiency
- d) Patients with a mechanical cardiac valvular prosthesis
- e) Patients with aortic stenosis

Question 3

What laboratory finding is required for the definitive diagnosis of endocarditis, in addition to endocardial involvement according to the Duke criteria?

- a) Leukocytosis with a left shift
- b) Identification of the causative organism by blood culture
- c) Elevated erythrocyte sedimentation rate
- d) Elevated serum procalcitonin concentration
- e) Elevated C-reactive protein concentration

Question 4

What is the advantage of transesophageal echocardiography in the diagnostic evaluation of suspected infective endocarditis?

- a) Greater sensitivity than transthoracic echocardiography for the detection of vegetations
- b) Identification of the causative organism
- c) Markedly better ability to diagnose right-heart endocarditis
- d) Determination of the composition of vegetations
- e) Reliable differentiation of degenerative and infective heart valve changes

Question 5

What is the main cause of negative blood cultures in endocarditis?

- a) Blood drawing outside a fever spike
- b) Infection with a rare pathogen
- c) Previously started antibiotic treatment
- d) Poor blood-drawing technique
- e) Concurrent treatment with cytostatic agents

Question 6

What infectious organism is the most common cause of early prosthetic valve endocarditis (i.e., in the first year after valve replacement surgery)?

- a) Staphylococcus aureus
- b) Chlamydia spp.
- c) Enterococcus faecium
- d) Organisms of the HACEK group
- e) Streptococcus spp.

Question 7

Which of the following distinctions is important for consideration before a broad-spectrum antibiotic therapy is started in a patient with infective endocarditis?

- a) Male vs female patient
- b) Mitral vs aortic valve endocarditis
- c) Patient younger or older than 75 years
- d) Native valve vs prosthetic valve endocarditis
- e) Symptom duration shorter or longer than 3 weeks

Question 8

Which of the following is an indication for immediate surgery in severe aortic or mitral insufficiency?

- a) Methicillin resistance
- b) Positive blood cultures for S. aureus
- c) Non-response of the infectious process to conservative treatment
- d) Enterococcal bacteremia
- e) Persistence of fever 3 or 4 days after the initiation of antibiotic treatment

Question 9

In what situation is outpatient treatment of infective endocarditis generally considered inadvisable?

- a) Left-heart endocarditis due to S. aureus
- b) Infection of the tricuspid valve
- c) When mitral insufficiency is present
- d) Infection of native heart valves with penicillin-sensitive streptococcal strains
- e) Outpatient treatment is generally considered inadvisable in all cases

Question 10

What antibiotic is the agent of choice to treat infective endocarditis caused by a methicillin-sensitive strain of S. aureus?

- a) Ampicillin
- b) Ceftriaxone
- c) Rifampicin
- d) Vancomycin
- e) Flucloxacillin

CONTINUING MEDICAL EDUCATION

Infective Endocarditis—Prophylaxis, Diagnostic Criteria, and Treatment

Nadja Westphal, Björn Plicht, Christoph Naber

E-REFERENCES

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